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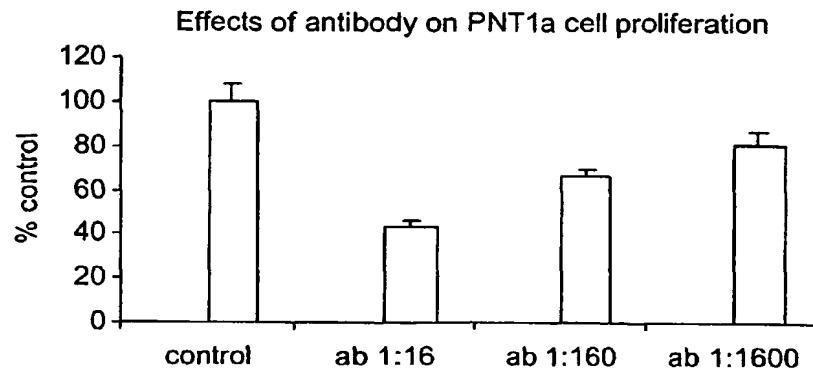
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[Continued on next page]

(54) Title: THERAPEUTIC USES OF MONOClonal ANTIBODIES TO THE ANGIOTENSIN-II TYPE-1 RECEPTOR



(57) Abstract: The use of monoclonal antibodies to the angiotensin-II type-I receptor is provided for the treatment of cancer and vascular smooth muscle cell proliferation. Specifically, use is provided of a monoclonal antibody or a fragment thereof to a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor defined by the sequence MILNSSTEDG IKRIQDDCPK AGRHNYIFVM IPTLYSIIFV VGIFG in the preparation of a medicament for the treatment of cancer or in the preparation of a medicament for the treatment of vascular smooth muscle (VSM) cell proliferation.

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MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

## INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/09186 A (VINSON GAVIN PAUL ;BARKER STEWART (GB); QUEEN MARY & WESTFIELD COL) 6 April 1995 (1995-04-06) page 1, paragraph 1 page 2, line 2 - line 4 page 5, line 2 - line 5 page 5, paragraph 4 - page 6, line 1 claims 9,10,12,13	1-11
A	page 3, line 18 - line 28 page 6, line 9 - line 20 ----- -/-	12,13

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the International filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the International filing date but later than the priority date claimed

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- "X" document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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## INTERNATIONAL SEARCH REPORT

PCT/GB 03/03758

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARKER S ET AL: "A monoclonal antibody to a conserved sequence in the extracellular domain recognizes the angiotensin II AT-1 receptor in mammalian target tissues" JOURNAL OF MOLECULAR ENDOCRINOLOGY, vol. 11, no. 2, 1993, pages 241-245, XP0009027454 & ISSN: 0952-5041 page 243, left-hand column, paragraph 4 - page 244, left-hand column, paragraph 1 page 244, right-hand column, line 1 - line 5 -----	1-11
Y	RICHARDS E M ET AL: "Inhibition of central angiotensin responses by angiotensin type-1 receptor antibody." HYPERTENSION. UNITED STATES JUN 1993, vol. 21, no. 6 Pt 2, June 1993 (1993-06), pages 1062-1065, XP009022991 ISSN: 0194-911X page 1063, right-hand column, paragraph 2 - page 1064, left-hand column, line 3 -----	1-11
Y	DE PAEPE BOEL ET AL: "Growth stimulatory angiotensin II type-1 receptor is upregulated in breast hyperplasia and in situ carcinoma but not in invasive carcinoma" HISTOCHEMISTRY AND CELL BIOLOGY, vol. 116, no. 3, September 2001 (2001-09), pages 247-254, XP002264864 ISSN: 0948-6143 abstract page 248, left-hand column, paragraph 3 page 252, right-hand column, line 19 - line 26 page 253, right-hand column, paragraph 2 page 253, right-hand column, line 58 - page 254, left-hand column, line 6 -----	1,3-6, 8-11
Y	TAHMASEBI M ET AL: "Transcription of the prorenin gene in normal and diseased breast" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 34, no. 11, October 1998 (1998-10), pages 1777-1782, XP004285130 ISSN: 0959-8049 page 1777, right-hand column, line 3 - line 8 page 1778, right-hand column, line 48 - line 56 page 1780, right-hand column, line 23 - line 29 -----	1,3-6, 8-11
	-/-	

## INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>INWANG E R ET AL: "Angiotensin II type 1 receptor expression in human breast tissues"          BRITISH JOURNAL OF CANCER,          vol. 75, no. 9, 1997, pages 1279-1283,          XP009022996          ISSN: 0007-0920          page 1282, left-hand column, paragraph 4 - right-hand column, paragraph 1</p> <p>-----</p>	1, 3-6, 8-11
X	<p>YANG BAICHUN C ET AL: "Increased angiotensin II type 1 receptor expression in hypercholesterolemic atherosclerosis in rabbits"          ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY,          vol. 18, no. 9, September 1998 (1998-09),          pages 1433-1439, XP002273166          &amp; ISSN: 1079-5642          page 1433, left-hand column, paragraph 1          page 1438, left-hand column, paragraph 3          page 1438, right-hand column, line 17 - line 24</p> <p>-----</p>	2-5, 7-10
Y	<p>LING SHANHONG ET AL: "Matrix-dependent gene expression of Egr-1 and PDGF A regulate angiotensin II-induced proliferation in human vascular smooth muscle cells"          HYPERTENSION (BALTIMORE),          vol. 34, no. 5, November 1999 (1999-11),          pages 1141-1146, XP002273079          &amp; ISSN: 0194-911X          abstract          page 1141, left-hand column, line 1 - line 5          page 1144, right-hand column, line 4 - line 7          page 1144, right-hand column, line 18 - line 21          page 1145, right-hand column, line 57 -          page 1146, left-hand column, line 2</p> <p>-----</p> <p style="text-align: center;">-/--</p>	2-5, 7-10

## INTERNATIONAL SEARCH REPORT

PCT/GB 03/03758

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>TOUYZ RHIAN M ET AL: "Angiotensin II stimulates DNA and protein synthesis in vascular smooth muscle cells from human arteries: Role of extracellular signal-regulated kinases" JOURNAL OF HYPERTENSION, vol. 17, no. 7, July 1999 (1999-07), pages 907-916, XP0009027461 &amp; ISSN: 0263-6352 page 907, left-hand column, line 5 - line 9 page 908, left-hand column, line 33 - line 39 page 908, left-hand column, line 50 - right-hand column, line 2 page 908, right-hand column, line 18 - line 24 page 915, left-hand column, paragraph 2</p> <p>-----</p>	2-5,7-10
A	<p>MURPHY T J ET AL: "ISOLATION OF A COMPLEMENTARY DNA ENCODING THE VASCULAR TYPE-1 ANGIOTENSIN II RECEPTOR" NATURE (LONDON), vol. 351, no. 6323, 1991, pages 233-236, XP002273150 &amp; ISSN: 0028-0836 figure 2</p> <p>-----</p>	12,13

## INTERNATIONAL SEARCH REPORT

PCT/GB 03/03758

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 6, 11 (completely) and, 3-5, 8-10 (partially)

The use of a monoclonal antibody directed against a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor or the use of said N-terminal portion of the angiotensin-II type-1 receptor in the preparation of a medicament for the treatment of cancer; a method of treating cancer using said monoclonal antibody.

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2. claims: 2 and 7 (completely) and, 3-5, 8-10 (partially)

The use of a monoclonal antibody directed against a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor in the preparation of a medicament for the treatment of vascular smooth muscle cell proliferation; a method of treating vascular smooth muscle cell proliferation using said monoclonal antibody.

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3. claims: 12, 13

A vaccine composition comprising a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 03/03758

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
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			AU 695074 B2	06-08-1998
			AU 7703294 A	18-04-1995
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			DE 69427484 T2	12-09-2002
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			US 6063620 A	16-05-2000